gression free survival (LPFS), event-free survival (EFS), toxicity, and patterns of failure. The sample size was determined so that the 95% confidence interval for the estimated 3-year OS would be ± 10% around expected value of 80%.

Results: Between July 2004 and January 2007, 65 patients were registered from 15 institutions. The patients characteristics were: male 45, female 20; median age 79 (range 50-91); median tumor size 21 mm (range 10–30 mm); adenocarcinomas 40, squamous cell carcinomas 21, others 4; and PS 0/1/2, 43/20/2. All patients completed the protocol treatment. As of November 2009, median follow-up of censored cases was 45.4 months. Of the eligible 64 patients, the 3-year OS was 76.0%, and the 3-year PFS, LPFS, and EFS were 54.5%, 68.5%, 51.4%, respectively. Grade 3 toxicities observed were chest pain in 1 (1.5%), dyspnea in 2 (3.1%), hypoxia in 1 (1.5%), and pneumonitis in 2 (3.1%). No grade 4 and 5 toxicity was observed. A total of 25 patients showed progressions of diseases including 11 local progressions.

Conclusions: SBRT for operable stage I NSCLC is highly effective with mild toxicity. This treatment has a potential to be an alternative to surgery and should be considered as a treatment option especially in elderly patients.

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ORAL ABSTRACT PRESENTATIONS

6

LACE-Bio: Cross-validation and Pooled Analyses of the Putative Prognostic/Predictive Biomarkers p27, p16 and cyclin E in IALT, ANITA, JBR10 and CALGB 9633

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Purpose/Objective(s): Platinum-based adjuvant chemotherapy (CT) improves survival in patients with completely resected non-small cell lung cancer (NSCLC). Predictive markers may improve the selection of patients for adjuvant CT. $P27^{Kip1}$ (p27), $p16^{INK4A}$ (p16) and cyclin E (CyE) are important regulators of cell cycle and potential markers of malignancy and response to chemotherapy. Previous studies in the IALT trial suggested that low p27 expression levels assessed by immunohistochemistry were predictive of chemotherapy benefit. The aim of the present study was to cross-validate the putative prognostic/predictive biomarkers p27, p16 and cyclin E.

Materials/Methods: LACE-BIO cross-validated the IALT p27 results in 669 patients (pts) from ANITA, JBR.10 and CALGB. Pooled analyses of IALT and JBR10 examined prognostic and predictive values of p16 and CyE in 1081 pts. High and low expression marker status was determined from IALT by the medians of intensity x positivity rate scores for p27 and CyE, and a score ≥ 1 for p16. Prognostic/predictive values of each marker for overall survival (OS) and disease-free survival (DFS) were tested in a Cox model stratified by trial and adjusted for clinical and pathological factors.

Results: 46% of pts had high p27 expression in their tumors, which was less common in squamous cell carcinomas (SCC) and T2 tumors. For OS, p27 status was neither prognostic (HR 0.97, 0.77-1.22, p=0.80), nor predictive of adjuvant CT benefit (interaction p=0.83, HR 0.83 vs. 0.87 for high and low p27, respectively). P27 status was also not prognostic or predictive for DFS. 45% of pts had high CyE and 42% had high p16. High CyE was more common in SCC ($p<0.0001$) while high p16 was more common among females ($p<0.0001$) and adenocarcinomas ($p<0.0001$). CyE and p16 were neither prognostic (HR 0.98 and 0.96, respectively) nor predictive for OS (interaction p=0.20 and p=0.95, respectively) and for DFS (interaction p=0.21 and p=0.79, respectively).

Conclusion: The prognostic and predictive values of p27, p16 or cyclin E in resected NSCLC were not confirmed. These results demonstrate the importance of robust validation of potential biomarkers prior to their use in clinical practice.

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7

Cytologic Evaluation of Stapled Lung Parenchyma Debris to Determine Adequate Surgical Margins

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Purpose/Objective(s): Pathologic evaluation of lung parenchyma margins is limited and imprecise and at times results in incorrect interpretation of surgical margins in NSCLC. We sought to evaluate staple line debris cytology in patients undergoing sub-lobar resections to determine if this novel technique is reliable in determining adequate or inadequate surgical margins.

Materials/Methods: A prospective trial evaluating staple line debris cytology in 72 patients undergoing diagnostic sub-lobar resection of the lung was performed at a single institution between November 2007 and June 2009. Spent stapler cartridges were mixed in 30cc of NS and served as the cytologic margin. Cytologic margin and surgical specimen were then evaluated separately and blinded to one another. Patients in whom sub-lobar resection was the planned definitive treatment were excluded from this study.

Results: Of 72 wedge specimens 41(57%) were NSCLC. In the 41 NSCLC specimens initial cytologic evaluation was positive in 8 (20%), surgical pathology margin was positive in 6(15%), both were positive in 3 (7%) of the cases. Subsequent unblinded review of both specimens resulted in changed interpretation of the surgical specimen from negative margin to positive margin in 3 (7%) of 41 cases. Analysis of staple debris cytology compared to histopathology demonstrated specificity (98%), sensitivity (78%), and overall accuracy (94%) using this technique.

Conclusions: Cytologic evaluation of staple line debris is a highly sensitive and specific test which alters the surgical margin interpretation in 7% of cases of NSCLC. This could be considered an adjunct to traditional pathologic reporting. With increasing utilization of sublobar resection for NSCLC, further study of the importance of staple line cytology is warranted.

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8

Bax Expression as a Predictive Marker of Survival Benefit in Non-small Cell Lung Carcinoma Treated by Adjuvant Cisplatin-based Chemotherapy

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land, [6]Department of Medicine, Centre R Gauducheau, St Herblain, France, [7]NCIC Clinical Trials Group and Queen's University, Kingston, ON, Canada, [8]Department of Medicine, Institut Gustave Roussy, Paris, France

Purpose/Objective(s): Because of its key role in mitochondrial apoptosis, it is hypothesized that Bax may be a mediator of chemotherapy response. To assess the impact of Bax expression on prognosis and benefit from platinum-based adjuvant CT (ACT), we undertook a pooled analysis of two randomized trials (IALT, JBR10).

Materials/Methods: Bax immunohistochemical (IHC) expression was assessed on slides obtained from formalin fixed paraffin embedded blocks, using automated immunostaining on Ventana immunostainer and a score of intensity x % of stained cells (1-300). The prognostic and predictive value for benefit from ACT of Bax IHC on overall survival (OS) and disease-free survival (DFS) was tested in a Cox model stratified by trial and adjusted for clinical and pathological variables.

Results: Bax IHC was successfully performed in 1080 out of 1135 slides (782 from IALT; 353 from JBR10). With a cut-off of score 90 (median), Bax was positive in 58 % of IALT and 26 % of JBR10 cases. There was no relation between Bax status and clinicopathological covariates including histology. In the control and chemotherapy arms combined, Bax status was not prognostic of OS or DFS in a Cox model adjusted for treatment, sex, age, revised histology, N or T stage ($p=0.84$ for OS; $p=0.55$ for DFS). There was no heterogeneity between the two trials ($p=0.08$ for OS; $p=0.26$ for DFS). Predictive value of Bax status on OS was tested in a multivariate Cox analysis. Bax status was significantly predictive for benefit from ACT on OS: hazard ratio (HR) of death in Bax negative patients: 1.13 [95%CI: 0.89 - 1.45] $p=0.31$; HR in Bax positive patients: 0.72 [0.56 - 0.91] $p=0.007$; test for interaction Bax/treatment: $p=0.009$ and no heterogeneity ($p=0.14$).Of note, 3/4 of the events corresponded to the IALT trial. Similarly, Bax status was significantly predictive for benefit of chemotherapy on DFS: HR in Bax negative patients: 1.08 [0.86 - 1.36] $p=0.52$; HR in Bax positive patients: 0.67 [0.53 - 0.84] $p=0.0006$; test for interaction Bax/treatment: $p=0.004$ and no heterogeneity ($p=0.22$). In view of these results the prognostic role of the Bax marker was evaluated in the control group; borderline significance for a small deleterious effect was observed on OS (HR = 1.28 [1.00-1.64], $p=0.05$) with a small deleterious effect on DFS (HR=1.33 [1.05 - 1.68], $p=0.016$); but this effect is not observed when subdividing the Bax marker into four quartiles ($p=0.098$ for OS and $p=0.11$ for DFS).

Conclusion: In this pooled analysis of the IALT and JBR10 randomized trials, Bax IHC was not significantly prognostic for survival, but was predictive of survival benefit from adjuvant cisplatin-based chemotherapy in surgically resected non small cell lung carcinoma. Supported by French Cancer League, Sanofi-Aventis and the Canadian Cancer Society Research Institute.

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9

Phase 2 Study of GI-4000 Vaccine as Adjuvant *Consolidation* Therapy Following Resection of Patients With Stage I-III Adenocarcinoma of the Lung With G12C, G12D, and G12V *KRAS* Mutations

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Purpose/Objective(s): All patients at MSKCC with adenocarcinoma of the lung undergo reflex testing for *EGFR* and *KRAS* mutations at the time of surgical resection. *KRAS* mutations occurred in 19% of resected lung adenocarcinomas from 2006- 4/2009. GI-4000 is a recombinant, yeast-based vaccine (S. cerevisiae) engineered to express one of 4 mutated RAS oncoproteins.

Materials/Methods: This study gave GI-4000 as adjuvant therapy to patients with stage I-III lung adenocarcinomas and G12C, G12D, or G12V *KRAS* mutations. All were disease free at their first post-treatment assessment 1–4 months after completing all standard therapies. GI-4000 was given for 3 weekly doses, then 6 monthly doses, then every 3 months for up to 3 years. The primary endpoint is vaccine-induced T cell responses documented by interferon-γ (IFN γ) ELISpot assay in peripheral blood mononuclear cells (PBMCs) stimulated *ex vivo* with RAS peptide pools from the specific *KRAS* mutation in the tumor specimens. Response criteria in baseline negative subjects: at least one *KRAS* peptide pool with increase from baseline of ≥ 25 IFNγ + cells/10^6 PBMCs and at least 2x the assay background. Response criteria in baseline positive subjects: baseline response of ≥ 25 IFNγ + cells /10^6 PBMCs and a ≥ 2 fold increase for that specific peptide pool on treatment and a second product related peptide response of ≥ 25 IFNγ + cells /10^6 PBMCs.

Results: We have accrued all 24 planned subjects. Women=17, Stage IA=10, IB=4, II=2, III=8, median age 67 (range 50-80), G12C=15, G12V=3, G12D=6, median # of doses per subject =9 (range 1-16). All patients received every vaccination, except for one due to unrelated surgical procedure. To date, there have been no serious adverse events related to GI-4000. An interim analysis of the 10 subjects with at least 6 months of immune sampling has been performed. Half of the subjects tested had either a treatment emergent response to the *ras* mutation in their tumor (3/6, 50%), or an improvement in a pre-existing baseline response to the mutation in their tumor (2/4, 50%) based on pre-specified immunologic criteria.

Conclusions: MSKCC's program of reflex (routine) testing of lung adenocarcinoma resection specimens for *EGFR and KRAS* mutations and the *EML4-ALK* fusion gene permits the identification of patients for *KRAS* specific therapy. The GI-4000 vaccine targeting mutated *KRAS* is immunogenic as an adjuvant "consolidation" therapy in patients with stage I-III lung adenocarcinomas harboring *KRAS* mutations. These data warrant further study of GI-4000 in *KRAS* mutant lung adenocarcinomas and other cancers with these specific mutations. (Supported by Marty's Fund, and GlobeImmune, Inc.).

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10

Prediction of Response to Gefitinib in NSCLC by EGFR Protein Expression is Increased by a Novel EGFR Antibody and the Use of AQUA Technology

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Purpose/Objective(s): Epidermal growth factor receptor (EGFR) protein expression is not recommended for predicting response to EGFR tyrosine kinase inhibitors. Previously reported data are based on antibodies (abs) targeting the external domain of the receptor. We assessed the predictive role of a novel ab targeting the intra-cellular domain of EGFR and compared it with extra-cellular specific abs. Owing to its epitope specificity the intracellular domain ab is purported to bind only activated EGFR. We further compared immunohistochemistry (IHC) vs automated quantitative fluorescence analyses (AQUA) (HistoRx).

Material/Methods: We evaluated EGFR protein expression with two abs specific for the extra-cellular domain (3C6, Ventana Medical Systems Inc; 31G7, Zymed) and one ab specific for the intracellular domain (5B7, VMSI) using IHC and AQUA on tissue microarrays of tumors from 70 Japanese non-small cell lung cancer (NSCLC) patients treated with gefitinib as monotherapy for their recurrent disease after surgery at the Tokyo Medical

University Hospital. We compared the predictive value of assessing EGFR expression by IHC, scoring membrane versus membrane + cytoplasm, and by AQUA, which automatically scores membrane + cytoplasm.

Results: EGFR expression evaluated by targeting the external domain of the receptor, with the 3C6 ab and IHC, was not predictive of response to gefitinib using either membrane staining (mean H score 34 vs 72, non responders vs responders, respectively, p=0.28) or both membrane + cytoplasm (43 vs 76, p= 0.27) but, it was borderline when using the 31G7 ab with AQUA (8.2 vs 8.9, p=0.0587). However, evaluation of EGFR expression using the internal domain specific ab 5B7 was significantly predictive for response to gefitinib using IHC and scoring membrane staining (185 vs 257, p=0.0095), more significant when considering both membrane + cytoplasm (179 vs 245, p=0.0035) and still slightly more significant when using 5B7 with AQUA (11.2 vs 12.7, p=0.0022). The positive predictive values for responders were 38, 40 and 50% and the negative predictive values were 83, 86 and 87%, when evaluating membrane with IHC, membrane + cytoplasm with IHC and AQUA, respectively. Progression-free survival was not significantly different between patients with high vs low EGFR expression (cut-off at the median), for any ab with either detection method.

Conclusion: EGFR expression determined by an ab (5B7) specific for the internal domain of the receptor is a significant and specific, but less sensitive, predictor of response to gefitinib in this cohort of Japanese NSCLC patients using IHC. Assessment of EGFR expression by AQUA increased the predictive performance of this ab and should be further explored for predicting response to EGFR inhibitors in NSCLC.

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11

A Novel Prognostic Transcriptional Signature for Early Stage Non-small Cell Lung Cancer

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Purpose/Objective(s): Lung cancer is the leading cause of cancer deaths in the U.S., with ~170,000 new cases diagnosed annually. Non-small cell carcinoma of the lung (NSCLC) accounts for 80% of lung cancer cases, and has a 5-year survival rate of only 15%. While adjuvant chemotherapy is the standard of care for patients with resectable stage II/IIIA disease, adjuvant chemo is not routinely offered in the stage I setting, despite the fact that 40% or more will relapse within 5 years post surgery. Currently, there are no clinico-pathological markers with sufficient power or utility to distinguish low- and high-risk cases of stage I NSCLC. A prognostic method capable of further stratifying stage I patients could define a subpopulation with substantially greater risk of disease recurrence that might show benefit from chemotherapy or serve as rational candidates for the testing of novel therapeutics in clinical trials.

Materials/Methods: We assembled a database of publicly available microarray expression profiles of stage I NSCLC tumors from four independent studies that together comprised >300 stage IA/IB patients. After correcting the RMA-normalized data for cohort-specific biases, we performed a statistically-guided meta-analysis of the gene expression datasets to construct and validate a gene-based classifier of prognosis.

Results: In a "training" cohort comprised of 120 patients, we identified a 6-gene prognostic classifier that stratified patients into low-, intermediate- and high-risk groups with significantly different relapse rates. The 6-gene stage I NSCLC classifier (aka, the "S1N" classifier) was then validated in a 179-patient "test" cohort. While the low- and intermediate-risk group survival times did not remain significantly different, the high-risk, poor outcome group showed strong agreement with the training cohort - with a 5-year relapse rate of >80%. We conclude that surgery followed by observation is not sufficient treatment for these high-risk stage I patients.

Conclusion: The 6-gene S1N classifier identifies a high-risk group of stage I patients for whom surgery alone is insufficient. High-risk patients identified by the S1N classifier may benefit from the chemotherapy offered to later stage patients.

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12

Identifying Clinically Relevant Cancer Genome Alterations in Lung Cancer: The Clinical Lung Cancer Genome Project Initiative

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The *Clinical Lung Cancer Genome Project* (*CLCGP*) was launched in 2007, bringing together scientists and physicians from a total of 13 medical and academic centers from Europe, Australia and the U.S. to perform the worldwide largest genomics analysis of clinically annotated lung cancer specimens. By now, the CLCGP has collected over 1,700 clinically annotated fresh-frozen lung cancer specimens of all subtypes. More than 900 specimens have already been extracted and genetic analyses have been performed on several hundred, including analyses of tumor suppressor gene and oncogene mutations and global analyses of chromosomal gene copy number. Among the first findings were the discovery of frequent *FGFR1* amplifications in squamous-cell lung cancer that associate with FGFR1 dependency (presented in a separate abstract) and many known as well as previously unknown correlations of cancer genome alterations with clinical outcome. Remarkably, the combination of global measures of copy number and analyses of gene mutations in such a large sample set has enabled for the first time to compare the prognostic value of individual alterations (e.g., *MYC* amplification vs. EGFR mutation) and of combinations of such lesions. Specifically, the groups of tumors characterized by mutations in the Ras-Raf signaling pathway in general had a worse prognosis than those characterized by alterations in receptor tyrosine kinase genes. By contrast, *FGFR1*-amplified lung cancers had a poor prognosis that correlated with the amplitude of the amplification. We note that our sample set is only biased by stage (predominantly surgically removed early cancers) but not by other epidemiological factors. Thus, while previous analyses of the prevalence of genetic alterations were typically biased by the preferential accrual of epidemiologically defined subgroups (e.g., adenocarcinomas of never smokers that have a higher chance of being EGFR-mutant, etc.), our cohort has enabled the identification of the actual prevalence of such alterations in naturally occurring cohorts of unprecedented size. Finally, the size of our collection afforded performing an in-depth genomic analysis of rare lung cancer subtypes as well. In small-cell lung cancer, we have identified novel recurrent somatic mutations by whole-exome sequencing of tumor-normal pairs. In summary, we have established a large collection of clinically annotated lung cancer specimens; initial genomics analyses of these tumors has revealed novel insights into lung cancer biology and genomic correlates of clinical phenotypes.

Author Disclosure Block: R. Thomas, None.

13

Effect of Race on Outcomes from Non-small Cell Lung Cancer

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Purpose/Objective(s): Lung cancer is the second most common cancer and also accounts for the most cancer-related deaths. Although racial disparities

in non-small cell lung cancer (NSCLC) outcomes in the United States have been well documented, their reasons are unclear. A retrospective analysis of patients included in the Veterans Affairs Central Cancer Registry (VACCR) was conducted to evaluate if these disparities were a function of the disease severity at presentation or a result of disparate treatments offered.

Materials/Methods: Patients diagnosed with NSCLC between January 1995 and February 2009, were identified. Data abstracted included age at diagnosis, gender, race, smoking history, disease stage, tumor grade, treatment and overall survival. Demographic data of according to race were compared using Kruskal-Wallis test or χ^2 test. Covariates associated with risk of mortality were evaluated using multivariate Cox proportional hazards regression. A p-value of 0.05 was considered significant.

Results: Data from 95,425 patients were analyzed. Of these, 93,840 (98%) were male and 78,207 (82%) were former or current smokers. These included 78,318 Caucasians (C), 16,433 African Americans (AA), 331 Asians (A) and 343 Native Americans (NA). C tended to have better risk features at presentation compared to AA [stages I or II combined (22% vs. 20%); grades I or II combined (18% vs. 16%)]. A larger proportion of C received recommended stage appropriate treatment compared to AA. For stage I, more C received surgery compared to other AA (46% vs. 40%; $p<0.001$). Similarly for stage IV, more C received chemotherapy compared to AA (23 vs. 19%; $p<0.001$). On multivariate analysis, race, age, stage at diagnosis and tumor grade were significantly associated with overall survival. AA had a lower risk of mortality compared to C (HR: 0.93, 95% CI; 0.91–0.95). No difference in risk of mortality were seen amongst A and NA when compared to C. When disease stage was considered, AA had a better median survival than C for stage III (9.1 vs. 8.6 months; $p=0.02$) and IV (4 vs. 3.6 months; $p<0.001$). No differences in survival among patients with stages I or II were seen according to race.

Conclusions: Although AA patients had a higher stage at presentation and worse grade, they had better overall survival compared to C, despite not receiving recommended stage appropriate treatment. This was more prominent in stage III and IV, where chemotherapy is an integral part of treatment, suggesting a better response to chemotherapy in AA compared to C. Genetic differences responsible for these differences should be investigated in order to better understand the effect of race on lung cancer biology and outcomes. In a single payer system, without access to care barriers, the previously described racial differences in lung cancer outcomes were not seen.

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14

TNM Staging Compared to Veterans Administration Lung Study Group Staging of Small Cell Lung Cancer- A Veterans Cancer Registry Analysis

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Purpose/Objective(s): Prior studies have shown the feasibility of utilizing the tumor, node, metastasis (TNM) staging system of non-small cell lung cancer in patients with limited stage small-cell lung cancer (L-SCLC) into well defined prognostic subgroups. We sought to evaluate the efficacy of the TNM staging system in sub-classifying patients with L-SCLC into varying prognostic groups.

Materials/Methods: Using the Veteran's Affairs Central Cancer Registry (VACCR) database, we conducted a survival analysis of patients with L-SCLC (excluding patients with M1 and N3 disease). T category, N status as per the sixth edition TNM staging, type of therapy, age, race, and tobacco history was analyzed. Kaplan-Meier analysis was used to calculate survival. Hazard ratios and 95% confidence intervals were calculated using Cox proportional-hazard model.

Results: Of 24,252 cases of SCLC in VACCR database diagnosed between 1995 and 2008, 7841 cases were eligible. These included 14% ($n = 1064$) patients with stage IA, 15% ($n = 1172$) stage IB, 2% ($n = 135$) IIA, 8% ($n = 593$) stage IIB and 28% ($n = 2212$) patients with stage IIIA. Median survival in years was 1.6 (95% CI, 1.47–1.72) for T1, 1.09 (95% CI, 1.04–1.13) for T2, 0.9 (95% CI, 0.83–0.97) for T3 and 0.72 (95% CI, 0.68–0.75) for T4 tumors ($p < 0.0001$). Increasing nodal stage also predicted for poor survival. Median survival in years was 1.22 years (95 % CI, 1.18–1.29) for N0, 1.06 (95% CI, 0.98–1.14) for N1 and 0.85 (95% CI, 0.82–0.89) for N2 disease ($p < 0.0001$). Stage specific survival in years was 1.90 (95% CI, 1.76–2.11) for stage IA, 1.21 (95% CI, 1.12–1.32) for stage IB, 1.41 (95% CI, 1.18–2.12) for stage IIA, 1.08 (95% CI, 0.97–1.21) for stage IIB, 0.96 (95% CI, 0.92–1.01) for stage IIIA, ($p < 0.0001$). Therapy was variable in this population; only 32% of patients received chemoradiation which is the standard of care for these patients. Median survival was 5.4 months (95%CI, 0.39–0.49) for patients who received no therapy, 10 months (95%CI, 0.80–1.89) for patients receiving chemotherapy only, 15 months (95%CI, 1.19–1.32) with chemoradiation, 11 months (95%CI, 0.85–1.02) with radiotherapy alone, 43 months (95%CI, 3.09–4.52) for patients who underwent surgery alone and 32 months (95%CI, 2.24–3.29) for patients who underwent surgery and received adjuvant therapy ($p < 0.0001$). In the multivariate analysis, TNM staging, type of therapy received, tumor grade and age at diagnosis were significantly associated with improved survival whereas race and tobacco history showed no association with median survival.

Conclusion: TNM staging system is successful in stratifying patients with limited SCLC into well defined prognostic groups.

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15

PET/CT-guided Involved-field Intensity Modulated Radiation Therapy for Limited-stage Small Cell Lung Cancer

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Purpose/Objective(s): The combination of intensity-modulated radiation therapy (IMRT) with positron emission tomography (PET) in the treatment of lung cancer allows radiation to be targeted to PET-positive areas of disease while sparing normal structures and reducing treatment-related toxicity. Compelling evidence suggests that omitting elective nodal irradiation does not compromise patient outcomes in non-small cell lung cancer, but whether the same is true for limited-stage small-cell lung cancer (LS-SCLC) remains controversial. We determined the frequency of elective nodal-field failure in patients with LS-SCLC staged with PET/CT and treated with involved-field IMRT.

Materials/Methods: Between 2005 and 2008, 62 patients with LS-SCLC at M. D. Anderson underwent disease staging with PET and were subsequently treated with an IMRT plan that did not intentionally include elective nodal stations in the planning treatment volume (PTV). In most cases, the prescribed dose was 45 Gy delivered in 30 twice-daily fractions (median dose 45 Gy in 30 fx, range 40.5 in 27 fx-63.8 in 35 fx) given with concurrent platinum-based chemotherapy. These patients were analyzed in follow-up for overall survival (OS), recurrence-free survival (RFS), and patterns of failure. In-field failure (IFF) was defined as recurrence or progression within the PTV. Extranodal failure (ENF) was defined as recurrence in initially uninvolved hilar, mediastinal, or supraclavicular nodes. Survival was assessed with the Kaplan-Meier method.

Results: Among the 62 patients included in the analysis, median age at diagnosis was 63 y (range 39-86 y). The median follow-up time was 21 months (range 4-58 months) among all patients and 26 months (range 4-58 months) among survivors. Median OS time and 2-year actuarial OS and RFS rates were 29 months, 63%, and 41%, respectively. Of the 32 patients with

recurrence, 22 (69%) had metastatic disease and 10 (31%) had locoregional failure. Among the latter group, 5 patients (16%) had IFF, 2 had ENF (6%), and 1 had isolated ENF (3%).

Conclusions: In this cohort of 62 patients with LS-SCLC staged with PET and treated with involved-field IMRT, isolated elective nodal failure occurred in only 1 patient (1.6%) and constituted 3% of observed failures. We conclude that elective nodal stations can be safely excluded in patients with LS-SCLC staged with PET for the purposes of dose escalation and reduced toxicity.

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16

Phase II Study of Sunitinib Monotherapy Following Irinotecan/Carboplatin as First-line Treatment for Patients with Extensive-Stage Small-Cell Lung Cancer

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Purpose/Objective(s): Inhibition of angiogenesis may be effective in the treatment of small-cell lung cancer (SCLC). Sunitinib, an oral agent that inhibits the VEGF signaling pathway, may delay progression in sequence with chemotherapy. The purpose of this phase II trial was to evaluate the efficacy and safety of sunitinib monotherapy following 6 cycles of irinotecan and carboplatin in patients with newly diagnosed extensive-stage SCLC.

Materials/Methods: Patients aged ≥18 years with previously untreated extensive-stage SCLC were eligible. Additional criteria included: ECOG PS 0–1, no active brain metastases, and adequate organ function. Patients received a maximum of six 28-day cycles of irinotecan (60mg/m^2 days 1, 8, 15) and carboplatin (AUC = 4, day 1), and were assessed for response every 8 weeks. After a maximum of 6 cycles of chemotherapy, patients with stable disease or better proceeded to sunitinib monotherapy (25mg po daily) until disease progression. The primary endpoint was 1-year overall survival (OS).

Results: Between 2/09 and 10/09, 34 patients (median age 65 years [range, 41-80]) were enrolled. 53% of patients were male, 47% had ECOG PS 0.21 patients (62%) completed 6 cycles of chemotherapy, and 17 (50%) initiated sunitinib monotherapy (median duration: 3 months (range: 1–8+ months). After a median follow-up of 50 weeks (range: 37–68 weeks), 22 (62%) of the patients remain alive; 6 patients are continuing on sunitinib monotherapy. The objective response rate with chemotherapy was 59%, and an additional 20% had stable disease. 1-year OS was 54% and median time to progression was 7.6 months. No grade 3/4 toxicities have occurred in >1 patient during sunitinib monotherapy.

Conclusions: This phase II trial provides support for further study of sunitinib maintenance therapy following platinum-doublet chemotherapy in patients with extensive-stage SCLC. The 1 year OS of 54% is encouraging, and a randomized trial would be appropriate to assess sunitinib's impact following chemotherapy.

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17

Phase II Study of Temozolomide for Relapsed Sensitive or Refractory Small Cell Lung Cancer (SCLC)

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Purpose/Objective(s): Alkylating agents have established efficacy in SCLC. Temozolomide is an oral alkylating agent that penetrates the CNS with the potential to treat brain metastases commonly seen in this disease. SCLC has aberrantly methylated *MGMT*, which is predictive of improved outcomes in patients with glioma treated with temozolomide. Anecdotal responses to temozolomide in patients with SCLC have been observed. Thus, we designed this phase II study of temozolomide in patients with relapsed SCLC.

Materials/Methods: Patients who have disease progression after one or two prior chemotherapy regimens and a Karnofsky performance status ≥ 60% are eligible. Temozolomide is administered at 75mg/m^2/day for 21 days of a 28-day cycle. The primary endpoint is ORR, which is assessed separately in two cohorts: sensitive-SCLC (S-SCLC) defined as relapse ≥60 days after first-line therapy, or refractory-SCLC (R-SCLC) defined as progression during first-line therapy, or within 60 days. In available tissue, we are assessing *MGMT* promotor methylation status by PCR and MGMT expression by immunohistochemistry.

Results: The accrual is complete for the R-SCLC cohort (N=16). 41 of the planned 48 patients have been accrued in the S-SCLC cohort. Temozolomide was second- and third-line treatment for 27 and 29 patients, respectively. 56% are women. 20 patients have progressive brain metastases, including 11 who had previously received brain radiation. Two of the 16 patients with R-SCLC have had a PR (ORR = 13%), one of whom was treated in third line; 5 patients have had SD. This met the pre-defined criteria for efficacy. 36 patients are assessable for response in the S-SCLC cohort, with an ORR of 25% (1 CR, 8 PR), four of whom were treated in third line; 10 patients have had SD. The ORR in both groups combined is 21%; while ORR is 26% and 18% in second- and third-line, respectively. Regressions in brain metastases have been observed in 10 patients, including 5 patients with progression after prior brain radiation. Toxicities include: grade 3/4 lymphopenia (30%); grade 3/4 neutropenia (4%); grade 3 thrombocytopenia (6%); grade 1/2 fatigue (60%); grade 1/2 emesis (34%); and grade 3 rash/pruritis (8%). Partial responses were noted in 29% of patients with *MGMT* promotor hypermethylation vs 9% with unmethylated tumors and in 43% of patients whose tumors were negative for MGMT expression vs 17% with positive MGMT expression (18 samples analyzed).

Conclusions: Single agent temozolomide has excellent efficacy in patients with SCLC, including those with refractory disease, in third-line, and in those with progressive brain metastases. This level of activity is comparable to, or better than, that of currently approved therapies, with less toxicity. Correlation of response with MGMT status is ongoing. Supported, in part, by Merck.

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18

OPTIMAL: Phase III Study of First-line Erlotinib Versus Gemcitabine Plus Carboplatin (GC) in Chinese Patients (pts) With Activating *EGFR* Mutation-Positive Advanced Non-small Cell Lung Cancer (NSCLC). On behalf of the OPTIMAL Investigators

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Purpose/Objective(s): Recent studies have demonstrated that epidermal growth factor receptor tyrosine-kinase inhibitors (EGFR TKIs) are particularly effective in NSCLC pts whose tumors harbor activating *EGFR* mutations (mut +ve). The phase III OPTIMAL study is a prospective evaluation of first-line treatment with the EGFR TKI erlotinib versus GC in Chinese pts with advanced NSCLC who have activating *EGFR* mut +ve disease.

Materials/Methods: Chemonaïve pts with advanced NSCLC and an ECOG PS of 0-2, measurable disease and confirmed exon 19 deletions or exon 21 L858R point mutations in *EGFR* were eligible. Pts were randomized (1:1; no cross-over was permitted) to receive erlotinib monotherapy (150mg/d) or gemcitabine (1000mg/m^2, d1 + d8) plus carboplatin (AUC=5, d1), every 3 weeks for up to 4 cycles, until unacceptable toxicity or progressive disease. The primary endpoint was progression-free survival (PFS). Secondary endpoints included overall survival (OS), safety, quality of life, and biomarker analyses, which are reported separately.

Results: Of the 549 pts screened, 186 had activating *EGFR* mut +ve disease. Of these pts, 165 were randomized to erlotinib (n=83) or GC (n=82). Baseline characteristics (including *EGFR* mutation type) were well-balanced across both treatment arms. In the safety analysis (n=155), no unexpected adverse events (AEs) were reported in either arm. The incidence and severity of treatment-related AEs and serious AEs (all grades) were lower in pts who received erlotinib (n=83; 79.5% & 2.4%, respectively) vs GC (n=72; 94.4% & 13.9%, respectively). A notably lower incidence of hematologic AEs (all grades) was observed in the erlotinib arm, compared with the GC arm: anaemia 4.8% vs 72.2%; neutropenia 6.0% vs 68.1%; thrombocytopenia 3.6% vs 63.9%, and febrile neutropenia 0% vs 1.4%, respectively. The incidence of treatment-related rash and diarrhea was higher in the erlotinib arm (rash 67.5% vs 19.4%; diarrhea 24.1% vs 2.8%, respectively), although most cases were mild to moderate (grade ≤2) in severity (1 pt each for rash and diarrhea [both grade 3] in the erlotinib arm; no grade 3-4 rash or diarrhea in the GC arm). No dose reductions or treatment withdrawals were necessary due to erlotinib-related rash. No interstitial lung disease-like events were reported. Efficacy analyses are underway.

Conclusions: In chemonaïve advanced NSCLC pts whose tumors had activating *EGFR* mutations, first-line erlotinib (150mg/d) had a favorable safety profile compared with GC. Full efficacy data will be presented at the meeting.

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19

Biomarker Associations With Survival for Refractory NSCLC Patients Receiving Erlotinib ± Sunitinib in a Randomized Phase 2 Trial

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Purpose/Objective(s): SUN1058 is a phase 2 study evaluating the efficacy and safety of sunitinib (SU) 37.5 mg/day as a continuous daily dose plus erlotinib (E) 150 mg/day vs. erlotinib (E) 150 mg/day plus placebo, in patients (pts) with platinum-refractory advanced NSCLC (Stage IIIB/IV, ECOG PS 0/1). Target enrollment was 126 pts to detect a 50% improvement in PFS.

Materials/Methods: Biomarkers analyzed to investigate the influence of tumor molecular characteristics on treatment outcome included EGFR protein expression, *EGFR* gene copy number, *EGFR* and *KRAS* mutational status, and RNA levels for targets of sunitinib and angiogenesis-associated proteins. Plasma soluble proteins levels were also assessed and included VEGF-A, sVEGFR-2, sVEGFR-3 and sKIT. P-values shown are not adjusted for multiple testing. Tumor biomarker data were available for a subset of pts.

Results: 132 pts were randomized. SU + E did not result in a statistically significant increase in PFS compared with E alone (12.3 weeks vs. 8.5 weeks; unstratified HR = 0.898, log-rank p>0.05). When comparing PFS between the two treatment arms in subgroups defined by tumor biomarkers, no statistically significant differences were observed in subgroups defined by either tumor EGFR status (protein expression: n=48 and n=48; gene copy number: n=31 and n=29; and mutation: n=25 and n=20, for SU + E and for E + placebo, respectively) or *KRAS* mutational status (n=28 and n=23). For pts with low tumor PDGFRα RNA levels, comparison of PFS favored the SU + E (n=16) vs. the E + placebo arm (n=11; HR=0.386, log-rank 1-sided p value: p=0.0401). However for pts with high tumor PDGFRα levels no such difference was observed. Plasma sVEGFR-2 and sVEGFR-3 levels decreased and plasma VEGF-A levels increased compared with baseline in the SU + E arm; no changes in these soluble proteins were seen in the E + placebo arm. In the SU + E arm, longer OS was associated with lower VEGF-C levels at baseline (HR=2.093, log-rank p=0.0347) and with smaller reductions in plasma sVEGFR-3 at Cycle 2 Day 1 (HR=0.439, p=0.04). In the E + placebo arm, longer PFS was associated with greater baseline plasma sKIT levels (HR=0.397, p=0.0061) and with greater reductions in plasma sVEGFR-3 at Cycle 2 Day 1 (HR=2.7187, p=0.0066) and Cycle 3 Day 1 (HR=2.919, p=0.011).

Conclusions: Comparisons of PFS between the 2 treatment arms in subgroups defined by EGFR and *KRAS* status did not result in any statistically significant differences in this phase 2 trial of SU + E vs. placebo + E in pts with advanced refractory NSCLC. Plasma levels of baseline VEGF-C and sKIT and of on-study sVEGFR-3 changes were associated with clinical outcome. A difference was observed between the 2 treatment arms in PFS favoring the SU + E arm for pts with low tumor PDGFRα RNA levels.

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20

Randomized Phase 2 Study of Ixabepilone (ixa) Plus Carboplatin (c) or Paclitaxel (p) Plus Carboplatin (c) in β3 Tubulin Overexpressing Non-small Cell Lung Cancer

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Purpose/Objective(s): Tumor expression of isoform β3T is an unfavorable prognostic factor in several tumor types, including NSCLC treated with standard tubulin-inhibiting chemotherapy agents. IXA is a semi-synthetic epothilone B analog with low susceptibility to multiple tumor resistance mechanisms in several tumor models. A randomized, international phase 2 study was conducted to explore if IXA-based chemotherapy can improve prognosis in patients (pts) with stage IIIb/IV NSCLC whose tumors are positive for β3T (β3T+).

Materials/Methods: 197 pts were randomized 1:1 and stratified by expression level of β3T status (positive/negative), to receive either IXA (32 mg/m^2) and C (AUC=6) (N=98) or P (200 mg/m^2) and C (AUC=6) (N=99) on Day 1 of a 21 day cycle (cyc) for up to 6 cyc. The primary endpoint compared PFS between IXA/C *vs* P/C in the β3T+ subgroup. The study was powered to detect a hazard ratio (HR) of 0.58 using a two-sided α=0.20 log-rank test with 90% power. β3T expression was measured in central lab on baseline tumor tissues using a standardized IHC assay developed by Dako; positivity was pre-defined as ≥50% of tumor cells classified as 2+ or 3+.

Results: There were 104 β3T+ and 93 β3T negative (β3T-) pts. 95 pts (52 β3T+ and 43 β3T-) received IXA/C and 96 pts (49 β3T+ and 47 β3T-) received P/C. Median PFS (mPFS) in the β3T+ subgroup was 4.3 mo in both arms (HR=1.04 [80% CI: 0.78, 1.41], p=0.853). In the βIII- subgroup, mPFS was 5.8 mo for Ixa/C *vs*. 5.3 mo for P/C (HR=0.78 [80% CI: 0.55, 1.10]). Independent of treatment arm, mPFS for pts with β3T+ was 4.27 mo [80% CI: 3.61, 5.42] and 5.59 mo (80% CI: 4.63, 6.47) for β3T- disease (HR=1.32 [80% CI: 1.06, 1.64]). IXA/C generally exhibited a similar safety profile to P/C. Peripheral neuropathy (all grades, grade 3/4) was numerically lower in the IXA/C arm (36.8%, 0%) *vs.* the P/C arm (56.3, 7.3%); however, a higher incidence of grade 3/4 anemia and thrombocytopenia (16.7% and 15.6%, respectively) were observed in the IXA/C arm relative to P/C (0% and 1.1%, respectively).

Conclusions: 1) IXA/C chemotherapy produced similar PFS and response as P/C in β3T+ and β3T- subgroups. 2) There was no predictive value of β3T for clinical activity (PFS or response) between IXA/C and P/C. 3) β3T+ patients had worse PFS relative to β3T-, regardless of treatment. 4) IXA/C was generally well tolerated in this study of first-line advanced NSCLC.

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21

The Influence of Epidermal Growth Factor Receptor Mutation on the Outcomes of NSCLC Patient After Radiotherapy

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Purpose/Objective(s): Epidermal growth factor receptor (EGFR) mutations are highly predictive of response to EGFR tyrosine kinase (TK) inhibitors in advanced non-small-cell lung cancer (NSCLC). However, we know little about the relationship between EGFR mutations and outcomes after radiotherapy. The purpose of this study is to evaluate the influence of EGFR mutation on outcomes of NSCLC after radiotherapy.

Materials/Methods: We retrospectively reviewed the pathological reports of NSCLC patients who underwent both EGFR testing and primary tumor radiotherapy between 2007 and 2009 in M.D. Anderson Cancer Center. Nucleotide sequencing of the kinase domain of EGFR (exons 18-21) was performed using nested PCR amplification of individual exons. Clinical outcomes were measured by local control, distant metastasis, and overall survival.

Results: There were 111 patients who underwent EGFR test as part of their pathological diagnostic procedure. The distribution of stages was: stage I in 4, stage II in 18, stage III in 82, stage IV in 7 patients. The median volume of gross tumor was 82.91cm^3, and the median dose of radiotherapy was 64.21Gy. Seventy-seven patients received concurrent chemoradiotherapy. The most common chemotherapy agents were carboplatin and etoposide. Thirty-four patients received radiotherapy only; and 19 patients received molecular targeted therapy including Tarceva. Among the 111 patients who had EGFR test, 24 had EGFR mutations. There were 2 cases with mutations in exon 18. Ten cases had mutation in exon 19 deletions. 1 case had mutation in exon 20. Eleven cases had mutation in exon 21. For the whole group, a presence of EGFR mutations was not associated with local control, distant metastasis, or overall survival compared to the wild-type group (p=0.6737, p=0.7355, p=0.5623) respectively. Since most of the mutations (21/24) were in exons 19 and 21, we also compared the difference of outcomes after radiotherapy between these two groups. There were no differences in patient demographics, including age, sex, stage, gross tumor volume, radiation dose, or treatment with EGFR-TK inhibitor between the two groups. There were significant differences between exon 19 group and exon 21 group in rates of local recurrence (0/10 vs 7/11, p=0.0021).There was no significant difference in distant metastasis and survival between the two groups (p=0,0870; p=0. 9187).

Conclusion: The most common loci of EGFR mutations are in exons 19 and 21 respectively. NSCLC with EGFR mutation in the exon 19 had more favorable disease control locally after radiotherapy. This finding, when validated in larger studies, could be used as a prognostic factor in designing personalize radiotherapy for NSCLC.

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POSTER DISCUSSION PRESENTATIONS

101

PET/CT and Outcome in Lung Cancer Treated With Stereotactic Body Radiation Therapy

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Purpose/Objective(s): Stereotactic body radiation therapy (SBRT) is becoming a standard treatment for medically inoperable stage I non-small cell lung cancer (NSCLC). However, the role of PET/CT in predicting clinical outcome after SBRT remains controversial, mainly because of residual PET avidity after treatment. We analyzed the prognostic value of PET/CT standardized uptake values (SUVs) in stage I and isolated lung-recurrent NSCLC treated with SBRT.

Materials/Methods: Patients with biopsy-proven stage I (n=68) or isolated lung parenchyma recurrent/secondary (n=60) NSCLC were treated with image-guided SBRT in an approved phase II clinical study. All patients underwent disease staging with PET/CT followed by 4-dimensional CT-based planning and daily CT-on-rail or cone-beam CT-guided SBRT. The prescribed dose was 50 Gy to the planning target volume, delivered in 4 consecutive days. Follow-up care comprised CT and clinical examination every 3 months for 2 years plus PET at 1-3 and 3.1-6 months and annually thereafter.

